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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,950	09/18/2001	Pramod B. Mahajan	35718/238971 (5718-142)	8514

826 7590 01/21/2004

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EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,950	MAHAJAN, PRAMOD B.	
	Examiner	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,11,13-16,19,20,23,27,28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,11,13-16,19,20,23,27,28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

STATUS OF THE APPLICATION

1. This Office action is in response to the Amendment and Remarks filed 30 October 2003.

2. The drawings were received on 30 October 2003, specifically Figure 2. The drawings are acceptable to the Examiner.

3. Those rejections not specifically addressed in this Office action are withdrawn in view of Applicant's amendments and/or remarks.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

5. Claims 10, 11, 13, 19, 20 and 27 are objected to because of the following informalities: The phrase "comprising(comprises) a nucleotide sequence of claim 1" should read -- comprising(comprises) the nucleic acid molecule of claim 1 --. Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27 and 28 remain rejected and claims 30-33 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility. This rejection is repeated for the reason of record as set forth in the last Office action mailed 30 July 2003. Applicant's arguments filed 30 October 2003 have been fully considered but they are not persuasive.

Applicant argues that rigorous correlation through mutant analysis is not necessary to confirm utility of Applicant's claimed sequences (page 19, 1st paragraph of the Remarks). Applicant argues that the statements of Jean *et al*, page 634, exhibit certainty on their part that they have identified a *MLH1* gene from *Arabidopsis* despite the lack of any informative mutant analysis (page 19, 2nd paragraph of the Remarks). This argument is not found to be persuasive because it is not pursuant upon a third party to establish a substantial utility upon Applicant's invention. Jean *et al* assert that they had isolated an *Arabidopsis* homologue of *MLH1* based upon a finding of 56% similarity to the human homologue, but also state that they had not definitively established the function of the isolated nucleic acid and state additional experimentation was required to analyze the function of the isolated gene (page 641, right column, last line). Applicant's assertion of function, and hence the utility of the claimed invention, is based upon similarity to the nucleic acid isolated by Jean *et al* (paragraph spanning pages 18-19 of the specification).

Applicant argues that based on "robust homology between the novel *MLH1* sequence of the invention and the *Arabidopsis MLH1* sequence" one of skill in the art would not doubt that Applicant's claimed sequences are *MLH1* sequences and that such sequences have a well-established utility in increasing the efficiency of targeted gene mutation and homologous recombination through the inhibition of the DNA mismatch repair system (page 20, 1st paragraph of the remarks). This argument is not found to be persuasive as addressed above. In addition, the art teaches that very little is known about the mismatch repair system in plants (Jean *et al*, 1997, page 641, left

column, 3rd paragraph). Hence, it remains unclear that one of skill in the art would know how to use the nucleic acid of the invention as Applicant claims.

Applicant has provided an alignment between SEQ ID NO: 2 and the PFAM domain sequence in Exhibit A. Applicant argues that it is well know in the art that regions of sequence homology with known functional domains may be used to determine protein function (page 20, 3rd paragraph of the Remarks). The Examiner has reviewed Exhibit A, which appears to be a query of amino acids 231-346 of SEQ ID NO: 2 with a DNA_mis_repair database. How this exhibit obviates this rejection is unclear. This amino acid region lies beyond the conserved N-terminal region of MLH1 homologous.

Claim Rejections - 35 USC § 112

7. Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27 and 28 remain rejected and new claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 30 July 2003. Applicant's arguments filed 30 October 2003 have been fully considered but they are not persuasive.

Applicant argues that a "rigorous standard" should not be applied to the instant invention and that sequence homology and presence of conserved domain(s) disclosed in the present application is sufficient to satisfy those of skill in the art that Applicant's sequence is a *MLH1* sequence (page 21, 4th paragraph and page 22 of the Remarks).

This argument is not found to be persuasive because it is Applicant's burden to establish a use of the claimed invention. In the case of Jean *et al*, there was an assumption made of function based on sequence identity and similarity of "conserved" amino acid sequences, but the art still recognizes that very little is known about the MMR system in plant, and thus how to use nucleic acids encoding putative polypeptides involved in said system. It is the Examiner's opinion that Applicant invites experimentation by one of skill in the art to establish the function and use of the claimed nucleic acid. At claims 4 and 5, the Examiner reiterates that Applicant has not taught one of skill in the art how to make and use isolated nucleic acid molecules that comprise fragments of SEQ ID NO: 1 or nucleic acids that encode a fragment of the amino acid sequence of SEQ ID NO: 2 as broadly claimed, or host cells comprising such nucleic acid molecules.

As directed to new claims 30-33, Applicant argues that these claims specify that the encoded polypeptide have mismatch repair activity. Applicant also argues that variants and fragments can be generated from the sequences of the invention in various ways, including amino acid substitutions, deletions, truncations, insertions and other mutagenesis techniques (page 23, 4th paragraph of the Remarks). Applicant argues that the specification provides guidance for altering the sequences of the invention, and that by alignment one of skill in the art can determine conserved regions unlikely to tolerate mutation or truncation (paragraph spanning pages 23-24 of the Remarks). Finally, Applicant argues that it is now customary in the art to make a number of sequences and to test them in a large-scale assay for desired function, which would not

be undue experimentation (page 24, 3rd paragraph of the Remarks). This argument is not found to be persuasive because Applicant has not established the function of the claimed nucleic acid as discussed supra. In addition, the Examiner emphasizes that very little is know about the MMR system in plants and hence very little is know on how to make and use variants of MMR system related polypeptides, and the nucleic acid(s) that encode them. The examiner notes that claim 30 encompasses an isolated nucleic acid molecules that encodes a protein that varies at, at least 108 amino acid positions, said positions being any of 19 other amino acids. Without specific guidance, it would have required undue trial and error experimentation by one of skill in the art at the time of Applicant's invention to make and use such variants.

8. Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims an isolated nucleic acid encoding a polypeptide having mismatch repair activity that is at least about 85-95% identical to SEQ ID NO: 1, encodes a polypeptide that is at least about 85-95% identical to SEQ ID NO: 2 or hybridizes to the nucleotide sequence show in SEQ ID NO: 1 said stringent conditions comprise hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C, and a nucleic acid molecule that has an antisense sequence of said nucleic acid.

Applicant describes a nucleic acid molecule that has the sequence of SEQ ID NO: 1 that encodes a polypeptide show in SEQ ID NO: 2.

Applicant does not describe the genus of nucleic acid molecules as claimed.

Hence, it is unclear that Applicant was in possession of the invention as broadly claimed.

Applicant argues that the recitation of at least 85% sequence identity is a very predictable structure of the sequences encompassed by the claimed invention and that the claims specify that the encoded polypeptide have mismatch repair activity, thereby providing a functional characterization of the sequences claimed in the genus (page 26, 3rd paragraph of the Remarks). This argument is not found to be persuasive because it remains unclear that Applicant has describe a nucleic acid that encodes a polypeptide having mismatch repair activity as discussed above.

Applicant argues that the instant claimed invention encompasses a genus defined by relevant identifying physical and chemical properties (page 27 of the Remarks). This argument is not found to be persuasive because the instant claims encompass a vast genus of nucleic acid of which Applicant has only describe a single genus. In particular, plant *MLH1* encoding nucleic acids have not be so well defined in the art as to enable one of skill in the art to recognize what Applicant has claimed in the instant invention.

See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-

recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. In the instant case, neither Applicant nor the art has not correlated the function with the structure as directed to putative plant *MLH1* encoding nucleic acids.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. The claims are free of the art which neither teaches nor suggests a nucleic acid encoding a mismatch repair protein having 85-100% sequence identity with SEQ ID NO: 1, or 85-100% sequence identity with SEQ ID NO: 2 or methods of using same.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (703) 306-4539, **(571) 272-0799 after 6 January 2004**. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (703) 306-3218, **(571) 272-0804 after 6 January 2004**. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

David H. Kruse, Ph.D.
2 January 2004